NON-TECHNICAL ABSTRACT

T lymphocytes lacking the normal common gamma chain receptor (γc) fail to proliferate in response to normal immunologic signals. Children born with mutations in the γc gene and who do not have a normally functioning common gamma chain receptor have severe combined immunodeficiency (SCID). Since the γc gene resides on the X chromosome, males are affected with this disease (referred to as X-linked severe combined immunodeficiency, X-SCID), since they have only a single X chromosome. Boys with X-SCID generally die in the first year of life from severe infections because they do not have an immune system which can fight infections. X-SCID can be cured by a bone marrow transplant, but this is an imperfect approach because many children do not having siblings who are tissue matches to serve as bone marrow donors. Transplanting bone marrow from a parent who is only a half match or from a non-family member may lead to significant problems, from rejection of the bone marrow graft to reaction of the donor's immune cells against the SCID patient. The current therapy for X-SCID includes injections of intravenous gamma globulin and antibiotic prophylaxis, which generally extends the life of patients. This therapy generally protects the children from infections. However, this costly treatment course must continue life-long or infections will ensue.

Gene transfer for X-SCID could be performed by introducing a normal copy of the human γc gene into the patient's blood-forming stem cells that are then transplanted back into the patient. Stem cells are present in bone marrow and also in the umbilical cord blood of newborns. Effective gene transfer for γc-deficient SCID will require inserting the normal human γc gene into a sufficient number of the subject's stem cells and expressing the gene to make surface receptor on the subject's immune blood cells.

In this study, we will determine whether this gene transfer approach is safe, feasible and effective. We will study twelve subjects, either newborn infants diagnosed prior to birth, or children, with X-SCID. Umbilical cord blood / bone marrow will be collected from the infants at birth / during childhood, processed in the laboratory to enrich for stem cells and introduce the normal human γc gene (using the MND-γc retroviral vector for gene delivery), followed by return of the cells to the subjects by an intravenous infusion. The infants will be started (and children maintained) on antibiotic prophylaxis and intravenous immunoglobulin (IVIG) therapy, because it is a known, effective therapy. We will examine blood samples taken on an approximately monthly basis for the next two years to evaluate side-effects from the procedure, whether the new γc gene is present in blood cells, and whether the new gene is working to make the common gamma chain receptor. If we determine that the γc gene is present and active in enough cells, we will wean the child from conventional prophylaxis and IG to determine whether the gene delivery has produced enough corrected cells to let the immune system be protective without the need for the conventional treatment.

These studies will provide information on the safety, feasibility and efficacy of this approach applying gene transfer for X-SCID. It may lead to a new treatment for this disease which is safer than bone marrow transplant and more cost-effective than life-long therapy with antibiotics and IVIG.